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A Review on Chemical Synthesis of Coumarin Derivatives and its Applications

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ABSTRACT

Coumarin (/ˈkuːmərɪn/) or 2H-chromen-2-one is an aromatic organic chemical compound with formula $C_9H_6O_2$. Its molecule can be described as a benzene molecule with two adjacent hydrogen atoms replaced by a lactone-like chain −(CH)=(CH)−(C=O)−O−, forming a second six-membered heterocycle that shares two carbons with the benzene ring. It can be placed in the benzopyrone chemical class and considered as a lactone.[1]Coumarin is a colorless crystalline solid with a sweet odor resembling the scent of vanilla and a bitter taste.[1] It is found in many plants, where it may serve as a chemical defense against predators. By inhibiting synthesis of vitamin K, a related compound is used as the prescription drug warfarin – an anticoagulant – to inhibit formation of blood clots, deep vein thrombosis, and pulmonary embolism.[1][2]
Keywords: coumarin, chemical, derivatives, applications, heterocycle, drug, warfarin, anticoagulant

1. INTRODUCTION

Coumarin is derived from *coumarou*, the French word for the tonka bean. The word *tonka* for the tonka bean is taken from the Galibi (Carib) tongue spoken by natives of French Guiana (one source for the plant); it also appears in Old Tupi, another language of the same region, as the name of the tree. The old genus name, *Coumarouna*, was formed from another Tupi name for tree, *kumarú*. Coumarin was first isolated from tonka beans in 1820 by A. Vogel of Munich, who initially mistook it for benzoic acid.[3][4]

Also in 1820, Nicholas Jean Baptiste Gaston Guibourt (1790–1867) of France independently isolated coumarin, but he realized that it was not benzoic acid.[5] In a subsequent essay he presented to the pharmacy section of the Académie Royale de Médecine, Guibourt named the new substance *coumarine*.[6][7]

In 1835, the French pharmacist A. Guillemette proved that Vogel and Guibourt had isolated the same substance.[8] Coumarin was first synthesized in 1868 by the English chemist William Henry Perkin.[9]

Coumarin has been an integral part of the fougère genre of perfume since it was first used in Houbigant's Fougère Royale in 1882.[10]

Coumarin can be prepared by a number of name reactions, with the Perkin reaction between salicylaldehyde and acetic anhydride being a popular example. The Pechmann condensation provides another route to coumarin and its derivatives, as does the Kostanecki acylation, which can also be used to produce chromones. Coumarin is found

naturally in many plants. Freshly ground plant parts contain higher amount of desired and undesired phytochemicals than powder. In addition, whole plant parts are harder to counterfeit; for example, one study showed that authentic Ceylon cinnamon bark contained 0.012 to 0.143 mg/g coumarin, but samples purchased at markets contained up to 3.462 mg/g, possibly because those were mixed with other cinnamon varieties.[12]

- Vanilla grass (*Anthoxanthum odoratum*)
- Sweet woodruff (*Galium odoratum*)
- Sweet grass (*Hierochloe odorata*)
- Sweet-clover (genus *Melilotus*)
- Tonka bean (*Dipteryx odorata*)
- Cinnamon; a 2013 study showed different varieties containing different levels of coumarin:[13]
  - Ceylon cinnamon or true cinnamon (*Cinnamomum verum*): 0.005 to 0.090 mg/g
  - Chinese cinnamon or Chinese cassia (*C. cassia*): 0.085 to 0.310 mg/g
  - Indonesian cinnamon or Padang cassia (*C. burmannii*): 2.14 to 9.30 mg/g
  - Saigon cinnamon or Vietnamese cassia (*C. loureiroi*): 1.06 to 6.97 mg/g
- Deertongue (*Carphephorus odoratissimus*),[14]
- Tilo (*Justicia pectoralis*),[15][16]
- Mullein (genus *Verbascum*)
- Many cherry blossom tree varieties (of the genus *Prunus*).[17]
- Related compounds are found in some but not all specimens of genus *Glycyrrhiza*, from which the root and flavour licorice derives.[18]

Coumarin is found naturally also in many edible plants such as strawberries, black currants, apricots, and cherries.[1]

Coumarins were found to be uncommon but occasional components of propolis by Santos-Buelga and Gonzalez-Paramas 2017.[19]

Coumarin and its derivatives are all considered phenylpropanoids.[11]

Some naturally occurring coumarin derivatives include umbelliferone (7-hydroxycoumarin), aesculetin (6,7-dihydroxycoumarin), herniarin (7-methoxycoumarin), psoralen and imperatorin.

4-Phenylcoumarin is the backbone of the neoflavones, a type of neoflavonoids.

Coumarin pyrazole hybrids have been synthesized from hydrazones, carbazones and thiocarbazones via Vilsmeier Haack formylation reaction. Compounds derived from coumarin are also called coumarins or coumarinoids; this family includes:

- brodifacoum[22][23]
- bromadiolone[24]
- difenacoum[25]
- auraptene
- ensaculin
- phenprocoumon (Marcoumar)
- PSB-SB-487
- PSB-SB-1202
- Scopoletin can be isolated from the bark of *Shorea pinanga*[26]
- warfarin (Coumadin)

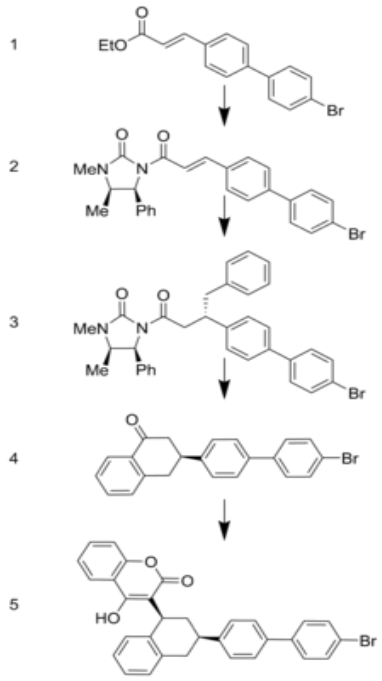
Coumarin is transformed into the natural anticoagulant dicoumarol by a number of species of fungi.[27] This occurs as the result of the production of 4-hydroxycoumarin, then further (in the presence of naturally occurring formaldehyde) into the actual anticoagulant dicoumarol, a fermentation product and mycotoxin. Dicoumarol was responsible for the bleeding disease known historically as "sweet clover disease" in cattle eating moldy sweet clover silage.[27][28] In basic research, preliminary evidence exists for coumarin having various biological activities, including anti-inflammatory, anti-tumor, antibacterial, and antifungal properties, among others.[27]

2. DISCUSSION

Brodifacoum is a derivative of the 4-hydroxy-coumarin group. Compounds numbers are found next to their respective compounds in the image below. Compound 1 is the starting ester needed to synthesize brodifacoum. To obtain this starting Compound 1, a simple Wittig condensation of ethyl chloroacetate with 4′-bromobiphenylcarboxaldehyde is accomplished. Compound 1 is transformed into Compound 2 by consecutive hydrolysis, halogenation to form an acid chloride, and then reacted with the required lithium anion. This is done using KOH and EtOH for hydrolysis, and then adding $SOCl_2$ for chlorination to form the acid chloride which reacts with the addition of lithium anion. Compound 2 is then transformed using organocopper chemistry to yield Compound 3 with good stereoselectivity of about 98%. Typically, a Friedel-Crafts type cyclization would then

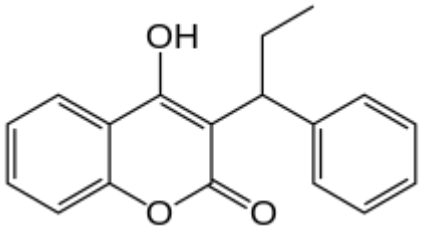
be used to obtain the two-ring system portion of Compound 4, but this results in low yield. Instead, trifluoromethanesulfonic acid in dry benzene catalyzes the cyclization with good yield. The ketone is then reduced with sodium borohydride yielding a benzyl alcohol. Condensation with 4-hydroxycoumarin under HCl yields Compound 5, brodifacoum.[4]

Phenprocoumon, a 4-hydroxycoumarin structurally similar to warfarin, is a white to off-white crystalline powder with a characteristic smell. It is practically insoluble in water, but soluble in chloroform, ethanol, methanol, and aqueous alkali hydroxide solutions. It is an acid (pK_a = 4.2) and melts between 177 and 181 °C (351 and 358 °F).[1] The substance is used as a racemic mixture; the *S*(−)-form is significantly more potent as an anticoagulant.[9]



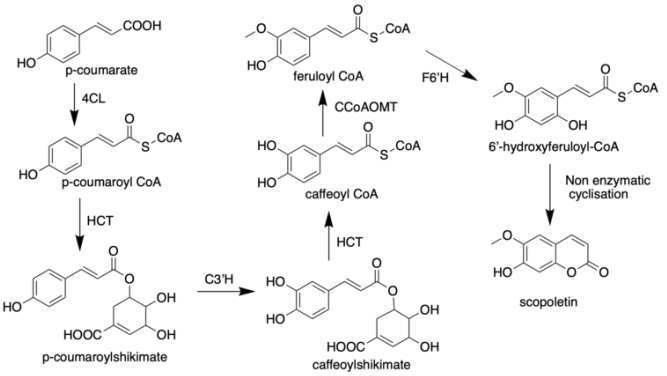
Stereospecific formation of Brodifacoum using an asymmetric organocopper compound.

Phenprocoumon (marketed under the brand names Marcoumar, Marcumar and Falithrom) is a long-acting blood thinner drug to be taken by mouth, and a derivative of coumarin.[2] It acts as a vitamin K antagonist and inhibits blood clotting (coagulation) by blocking synthesis of coagulation factors II, VII, IX and X. It is used for the prophylaxis and treatment of thromboembolic disorders such as heart attacks and pulmonary (lung) embolism. The most common adverse effect is bleeding. The drug interacts with a large number of other medications, including aspirin and St John's Wort. It is the standard coumarin used in Germany,[3] Austria,[4] and other European countries.[5]



Phenprocoumon

Scopoletin is a coumarin found in the root of plants in the genus *Scopolia* such as *Scopolia carniolica* and *Scopolia japonica*, in chicory, in *Artemisia scoparia*, in the roots and leaves of stinging nettle (*Urtica dioica*), in the passion flower, in *Brunfelsia*, in *Viburnum prunifolium*, in *Solanum nigrum*,[1] in *Datura metel*,[2] in *Mallotus resinosus*,[3] or and in *Kleinhovia hospita*. It can also be found in fenugreek,[4] vinegar,[5][4] some whiskies or in dandelion coffee. A similar coumarin is scoparone. Scopoletin is highly fluorescent when dissolved in DMSO or water and is regularly used as a fluorimetric assay for the detection of hydrogen peroxide in conjunction with horseradish peroxidase. When oxidized, its fluorescence is strongly suppressed.

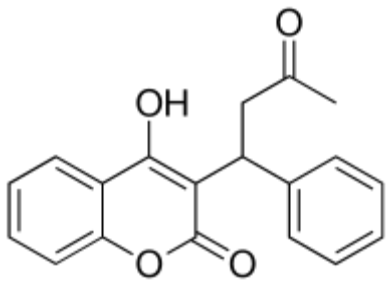


4CL: 4-coumaroyl CoA ligase, HCT: hydroxycinnamoyl transferase, C3'H: cinnamoyl ester 3'-hydroxylase
CCoAOMT: caffeoyl CoA O-methyltransferase, F6'H: feruloyl-CoA 6'-hydroxylase

Scopolin is a glucoside of scopoletin formed by the action of the enzyme scopoletin glucosyltransferase.

Warfarin is an anticoagulant used as a medication under several brand names including Coumadin,[8] and as a poison for rats and other pests.[9][10] While the drug is described as a "blood thinner", it does not reduce viscosity but inhibits coagulation, and is commonly used to prevent blood clots in the circulatory system such as deep vein thrombosis and pulmonary embolism, and to protect

against stroke in people who have atrial fibrillation, valvular heart disease, or artificial heart valves.[8] Less commonly, it is used following ST-segment elevation myocardial infarction and orthopedic surgery.[8] It is usually taken by mouth, but may also be administered intravenously.[8]



The common side effect, a natural consequence of reduced clotting, is bleeding.[8] Less common side effects may include areas of tissue damage, and purple toes syndrome.[8] Use is not recommended during pregnancy.[8] The effects of warfarin are typically monitored by checking prothrombin time (INR) every one to four weeks.[8] Many other medications and dietary factors can interact with warfarin, either increasing or decreasing its effectiveness.[8][11] The effects of warfarin may be reversed with phytomenadione (vitamin K_1), fresh frozen plasma, or prothrombin complex concentrate.[11]

Warfarin decreases blood clotting by blocking vitamin K epoxide reductase, an enzyme that reactivates vitamin K_1.[11] Without sufficient active vitamin K_1, clotting factors II, VII, IX, and X have decreased clotting ability.[11] The anticlotting protein C and protein S are also inhibited, but to a lesser degree.[11] A few days are required for full effect to occur, and these effects can last for up to five days.[8][12] Because the mechanism involves enzymes such as *VKORC1*, patients on warfarin with polymorphisms of the enzymes may require adjustments in therapy if the genetic variant that they have is more readily inhibited by warfarin, thus requiring lower doses.[13][14]

Warfarin first came into large-scale commercial use in 1948 as a rat poison.[15][9] It was formally approved as a medication to treat blood clots in humans by the U.S. Food and Drug Administration in 1954.[8] In 1955, warfarin's reputation as a safe and acceptable treatment was bolstered when President Dwight D. Eisenhower was treated with warfarin following a massive and highly publicized heart attack.[16] Eisenhower's treatment kickstarted a transformation in medicine whereby coronary artery disease, arterial plaques, and ischemic strokes were treated and protected against by using anticoagulants such as warfarin. It is on the World Health Organization's List of Essential Medicines.[17][18] Warfarin is available as a generic medication[19] and under many trade names.[1] In 2020, it was the 58th most commonly prescribed medication in the United States, with more than 11 million prescriptions.[20][21]

3. RESULTS

Difenacoum was first introduced in 1976 as a rodenticide effective against rats and mice which were resistant to other anticoagulants.[2] Auraptene is a natural bioactive monoterpene coumarin ether. It was first isolated from members of the genus *Citrus*.Auraptene has shown some effect as a chemopreventative agent against cancers of liver, skin, tongue, esophagus, and colon in rodent models.[1] Phenprocoumon is used for the prophylaxis and treatment of thromboembolic disorders after heart bypass surgery and myocardial infarction (heart attack), long-term treatment of myocardial infarction with increased risk of thromboembolism, thrombophilia (abnormal blood clotting), antithrombin III deficiency, atrial fibrillation (a kind of abnormal heart rhythm) with artery embolisms, after venous thrombosis, pulmonary embolism and artificial heart valve surgery, as well as chronic ventricular aneurysm (bulging of the heart wall) and congestive cardiomyopathy (enlarged heart).[1] When phenprocoumon therapy is started, the clotting tendency of the blood is measured daily by determining the prothrombin time, more specifically the international normalized ratio (INR). After the desired INR has been reached, which typically takes five to six days, intervals between measurements are increased to twice or three times a week for a week or two, then to two to four weeks if the patient is stable. INR monitoring continues throughout the therapy, often for life.[1][4] This is necessary because people need different doses depending on the genetic makeup of their enzymes, activity of coagulation factors, vitamin K concentrations in the body, other drugs, and diet.[2][6]

If a fast onset of action is needed, as after an acute thromboembolism, phenprocoumon therapy has

to be accompanied with a subcutaneous or intravenous low-molecular-weight heparin (LMWH) for the first 36 to 72 hours. Similarly, if the blood thinning effect has to be stopped before a surgery, phenprocoumon is paused up to two weeks beforehand, and the therapy gap is "bridged" with LMWH until after the surgery. Alternatively, phenprocoumon can be antagonised with vitamin K, for example before an unplanned surgery, or when severe bleeding occurs after overdosing.[1][4]

Warfarin is used to decrease the tendency for thrombosis, or as secondary prophylaxis (prevention of further episodes) in those individuals who have already formed a blood clot (thrombus). Warfarin treatment can help prevent formation of future blood clots and help reduce the risk of embolism (migration of a thrombus to a spot where it blocks blood supply to a vital organ).[22]

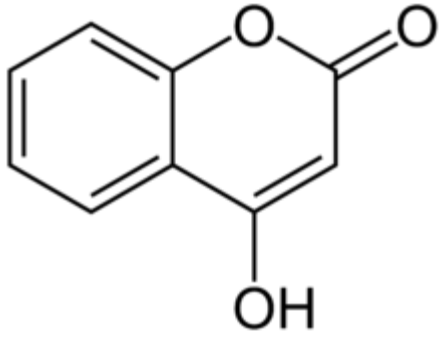
Warfarin is best suited for anticoagulation (clot formation inhibition) in areas of slowly running blood (such as in veins and the pooled blood behind artificial and natural valves), and in blood pooled in dysfunctional cardiac atria. Thus, common clinical indications for warfarin use are atrial fibrillation, the presence of artificial heart valves, deep venous thrombosis, and pulmonary embolism (where the embolized clots first form in veins). Warfarin is also used in antiphospholipid syndrome. It has been used occasionally after heart attacks (myocardial infarctions), but is far less effective at preventing new thromboses in coronary arteries. Prevention of clotting in arteries is usually undertaken with antiplatelet drugs, which act by a different mechanism from warfarin (which normally has no effect on platelet function).[23] It can be used to treat people following ischemic strokes due to atrial fibrillation, though direct oral anticoagulants (DOACs) may offer greater benefits.[24]

Warfarin – a coumarin – with brand name, *Coumadin*, is a prescription drug used as an anticoagulant to inhibit formation of blood clots, and so is a therapy for deep vein thrombosis and pulmonary embolism.[2][29] It may be used to prevent recurrent blood clot formation from atrial fibrillation, thrombotic stroke, and transient ischemic attacks.[29]

Coumarins have shown some evidence of biological activity and have limited approval for few medical uses as pharmaceuticals, such as in the treatment of lymphedema.[1][30] Both coumarin and 1,3-indandione derivatives produce a uricosuric effect, presumably by interfering with the renal tubular reabsorption of urate.[31] Coumarin is used in the pharmaceutical industry as a precursor reagent in the synthesis of a number of synthetic anticoagulant pharmaceuticals similar to dicoumarol.[1] 4-hydroxycoumarins are a type of vitamin K antagonist.[1] They block the regeneration and recycling of vitamin K.[1][29] These chemicals are sometimes also incorrectly referred to as "coumadins" rather than 4-hydroxycoumarins. Some of the 4-hydroxycoumarin anticoagulant class of chemicals are designed to have high potency and long residence times in the body, and these are used specifically as rodenticides ("rat poison").[1] Death occurs after a period of several days to two weeks, usually from internal hemorrhaging. Coumarin dyes are extensively used as gain media in blue-green tunable organic dye lasers. Among the various coumarin laser dyes are coumarins 480, 490, 504, 521, 504T, and 521T.[34] Coumarin tetramethyl laser dyes offer wide tunability and high laser gain,[35][36] and they are also used as active medium in coherent OLED emitters. and as a sensitizer in older photovoltaic technologies.[38] Coumarin is often found in artificial vanilla substitutes, despite having been banned as a food additive in numerous countries since the mid-20th century. It is still used as a legal flavorant in soaps, rubber products, and the tobacco industry,[1] particularly for sweet pipe tobacco and certain alcoholic drinks.

4. CONCLUSIONS

4-Hydroxycoumarin is an important fungal metabolite from the precursor coumarin, and its production leads to further fermentative production of the natural anticoagulant dicoumarol.



This happens in the presence of naturally occurring formaldehyde, which allows attachment of a second 4-hydroxycoumarin molecule through the linking carbon of the formaldehyde, to the 3-position of the first 4-hydroxycoumarin molecule, to give the semi-dimer the motif of the drug class. Dicoumarol appears as a fermentation product in spoiled sweet clover silages and is considered a mycotoxin.[1]

4-Hydroxycoumarin

is biosynthesized from malonyl-CoA and 2-hydroxyben zoyl-CoA by the enzyme 4-hydroxycoumarin synthase.[2] After the identification of dicoumarol and its anticoagulant activity, it became the prototype for a class of drugs. 4-Hydroxycoumarin forms the core of the chemical structure of anticoagulants known collectively as 4-hydroxycoumarins. They include, for example, warfarin, a pharmaceutical drug used to prevent formation of blood clots, and brodifacoum, a widely used rodenticide.

Conflict of interest statement

Authors declare that they do not have any conflict of interest.

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